Critical Care Medicine
April 2026 • Volume 54 • Number 4 • Pages 983–994

ROAD TO PRECISION

What Is Sepsis, Who Gets It, How, and Why? The Keys to Unlocking Precision Medicine in Sepsis

Elizabeth A. Gay, MD[1]
Nuala J. Meyer, MD, MS[2]
Pratik Sinha, MB ChB, PhD[3]

Due to its nonspecific clinical criteria, sepsis is clinically, microbiologically, pathophysiologically and immunologically highly heterogeneous. Consequently, despite hundreds of clinical trials, no host-targeted therapy has been shown to be ubiquitously efficacious, leading investigators to pursue more precision-based approaches for enriching sepsis populations through the identification of subgroups or phenotypes. Here, we review the myriad domains in which heterogeneity is observed in sepsis and the challenges and opportunities they offer to improve outcomes. We review current strategies used by investigators leveraging novel biological measurements and/or computational algorithms to identify more homogeneous subgroups either based on pathogen or host characteristics or both. Finally, we review some of the most promising recent advances that seek to bring these complex and innovative discoveries to the bedside to facilitate precision medicine in sepsis.

KEYWORDS: acute respiratory distress syndrome; endotypes; phenotypes; precision medicine; sepsis; subphenotypes

Sepsis is highly prevalent and represents a massive burden on global health (1). Conceptually defined as a dysregulated systemic response to infection, sepsis is currently diagnosed using bedside markers of organ failure as specified in the Sepsis-3 consensus statement (2). The advent of antibiotics (3), vaccines (4), improved population-wide sanitation (5), promptness of source control (6), increased awareness among the public and healthcare providers (7), and improved early supportive care (8) have all led to improved outcomes in sepsis (9).

Despite prompt and appropriate antimicrobials and source control, many patients with sepsis have persistent organ failure and mortality exceeding 30% (10–12). Those who survive frequently experience lasting impairment in their physical, emotional, and cognitive health (12–16). In hundreds of trials, investigators have sought to modify the host response in sepsis but failed to improve survival or reduce long term disabilities, a failure often attributed to the nonspecific study enrollment criteria (17, 18), and our limited ability to rapidly characterize infection response in the context of each patient (19–21).

Motivated by these failures, and with observed successes in cancer and asthma trials (22, 23), investigators are increasingly pursuing precision-based approaches in sepsis. Precision medicine seeks to enrich populations to increase the probability of detecting a treatment effect, should one exist. Broadly, these approaches can be categorized into "prognostic enrichment," where the population is enriched for an outcome of interest, such as using Pao_2/Fio_2 to enrich for mortality in the Proning Severe ARDS Patients (PROSEVA) trial (24); or "predictive enrichment," where populations are enriched for treatment

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DOI: 10.1097/CCM.0000000000007043

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responsive characteristics, classically exemplified by the use of trastuzumab in human epidermal growth factor receptor-2 positive breast cancer (25). Increased access to computational power, alongside high dimensional molecular measurements collectively called "omics," have spurred an exponential rise in precision-based investigations in sepsis. While these discoveries are exciting and have the potential to improve outcomes, to date, none has changed practice.

DOMAINS OF HETEROGENEITY–OPPORTUNITIES FOR PRECISION

Definition

The most recent consensus (Sepsis-3) describes sepsis as, "life-threatening organ dysfunction caused by a dysregulated host response to infection" (2). The terms "life-threatening," "dysregulated host response," and "infection" are all subjective, illustrating the potential for heterogeneity. The response that pathogens evoke, including the ensuing release of pro- and anti-inflammatory mediators, endothelial activation and disruption, and coagulopathy (**Fig. 1**), as well as the resultant end-organ damage, are all nonuniform, on a continuous scale, and lead to nonlinear multifactorial interactions that are challenging to predict.

Nevertheless, the last 5 decades has seen an explosion of studies seeking to enhance our understanding of the pathophysiology and immunobiology of sepsis (26, 27). The disappointing translation of these discoveries to practice may, in part, be because our understanding of sepsis has largely been garnered through experimental studies with controlled infectious insults in genetically uniform animals or cell culture models. By contrast, clinical trials are often based on broad nonspecific criteria, such as those outlined in Sepsis-3, which capture myriad pathogens and host responses that are driven by diverse genetic variations, environments, and lifestyle-dependent exposures (19). Better categorization of sepsis that bridges this dichotomy through incorporation of infection characteristics and host response offers an intuitive route to precision medicine in sepsis.

Microbes

A frequently overlooked feature in our sepsis framework is the contribution of the pathogens. Other than acknowledging its presence, Sepsis-3 overlooks all other aspects of the pathogen. Further, while bacteria are recognized as the principal causative organisms of sepsis, increased surveillance is broadening our understanding that viruses frequently lead to sepsis as well (28, 29). In bacterial sepsis, the pathogen is seldom considered in clinical decision-making beyond antibiotic choice. This is despite a growing body of evidence suggesting bacterial species elicit distinct host immune responses as measured by single-cell and bulk transcriptomics and proteins (30, 31). Pathogen-associated molecular patterns (PAMPs) and the host pattern recognition proteins that they interact with differ according to bacterial characteristics. Classically, Gram-negative PAMPs (e.g. lipopolysaccharide) interact with toll-like receptor (TLR)-4, and Gram-positive bacteria PAMPs (e.g., lipoteichoic acid) are detected by TLR-2, with each activating distinct downstream intracellular signaling cascades (32), leading to distinct protein and transcriptomic signatures and microvascular injury patterns (33–36).

Given that critically ill patients with sepsis are typically assessed well after the initial pathogen exposure, and the pathogen is often unidentified, the observed dysregulated host responses likely reflect the biology of organ failure and critical illness rather than pathogen-specific effects (37, 38). Pathogen and host molecular signatures, if characterized rapidly, may represent a potential route for precision therapy. To this end, two recent studies demonstrate the promise of integrating host and microbial genomics for improving lower respiratory tract infection (LRTI) and sepsis diagnosis. In LRTI, a combined classifier from tracheal aspirates (pathogen, microbiome, and host transcriptome) achieved 100% negative predictive value for diagnosis, outperforming each individual component (39). In sepsis, a plasma-based combined metagenomic and host transcriptomic model identified 99% of microbiologically confirmed cases and predicted sepsis in most suspected or indeterminate cases (40). While limited by small sample sizes and inherent diagnostic uncertainty of sepsis, these studies highlight the potential of genomics to enhance sepsis specificity.

The Host

When viewed from an individual's lifetime exposure to microbes, sepsis is an incredibly rare occurrence. Exploring why individuals develop sepsis when exposed to microbes they have previously been able to

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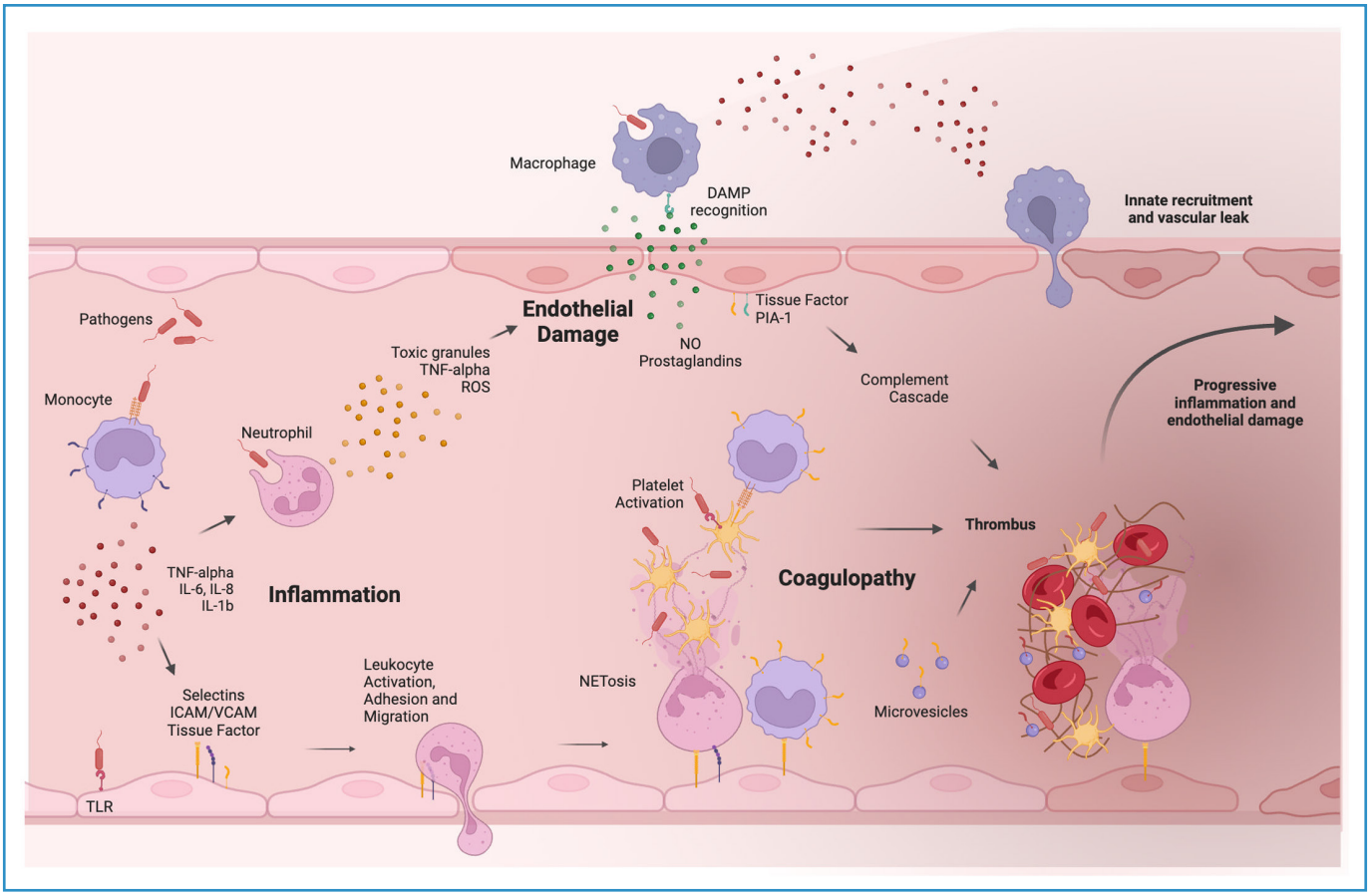

Figure 1. Overview of the pathophysiology of sepsis that includes inflammation, endothelial dysfunction, and coagulopathy. DAMP = damage-associated molecular pattern, ICAM = intercellular adhesion molecule, IL-1b = interleukin-1 beta, IL-6 = interleukin-6, IL-8 = interleukin-8, NETosis = neutrophil extracellular trap formation, NO = nitric oxide, PAI-1 = plasminogen activator inhibitor-1, ROS = reactive oxygen species, TLR = toll-like receptor, TNF-α = tumor necrosis factor alpha, VCAM = vascular cell adhesion molecule. (Adapted from Gay B, BioRender.com, 2026; https://BioRender.com/ krlqux7).

eliminate may offer novel therapeutic opportunities. Death from infection is a highly heritable trait (41), and the observation that specific pathogens plague patients with inherited errors of immunity (42) highlights the impact of genetic variation on both sepsis risk and outcome. However, relatively few genetic variants that strongly influence sepsis mortality have been validated in large populations, and of those which have replicated, several are extremely rare (**Table 1**) (43–45).

The host response in sepsis is inherently dynamic, shaped by therapeutic interventions, source control, supportive care, and the passage of time. Because patients present at different stages of illness, these temporal dynamics constitute an additional and often underappreciated dimension of biological heterogeneity in sepsis. Conceptual models of the temporal kinetics of the immune system are being purported that include two broad immune states (**Fig. 2**): 1) hyperinflammatory—characterized by increased inflammatory cytokines, innate immune activation, endothelial injury, and manifesting the classically described dysregulated systemic response of sepsis (48); and 2) immunosuppressed—which is exemplified by T- and B-cell exhaustion, hypofunctional myeloid cells, increased apoptosis of other immune cells, and reprogramming of macrophages and monocytes (49). In this conceptual model, persisting longitudinally in either state leads to adverse outcomes, and resolution of either state is contingent on returning to an immune set-point compatible with life. Despite being described over 2 decades ago, operationalizing these immune states into clinical entities has been challenging (50). Further, these states may not be mutually exclusive, and such is the multidimensional complexity of sepsis that patients can be hyperinflammatory based on protein signatures, while immunosuppressed based on transcriptional signatures (51, 52).

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TABLE 1.
Replicated Genome-Wide Associations for Sepsis 28-Day Mortality

Gene Variant	Population	Minor Allele Frequency[a]	OR for Mortality (95% CI)[b]	References
FER rs4957796	1553 EA pneumonia	0.187	0.56 (0.45–0.69); $p = 5.6 \times 10^{-08}$	Rautanen et al (43)
SAMD9 rs34896991	687 EA sepsis discovery; 1362 EA and 702 African ancestry sepsis validation	0.018	1.64 (1.37–6.78); $p = 4.9 \times 10^{-08}$	Hernandez-Beeftink et al (44)
SLC5A12/FIBIN rs146257041		0.015	0.89 (0.12–6.39); $p = 3.0 \times 10^{-09}$	
MIR3169 rs138347802		0.014	2.57 (1.82–13.0); $p = 4.44 \times 10^{-08}$	
VSP13A rs117983287	1636 EA sepsis (740 from trial, 936 pneumonia cohort)	0.01	18.2 (95% CI, not reported); $p = 2.4 \times 10^{-10}$	Scherag et al (45)

EA = European ancestry, OR = odds ratio.
[a]Minor allele frequency (MAF) in noncase population, where higher values represent more common variants. MAF 0.01 indicates 1% of the population carry the variant allele.
[b]ORs shown are for the meta-analysis effect estimate for 28-d mortality; color coding indicates the direction of the association, with blue indicating a lower odds and red indicating a higher odds of death.
Genes are listed by Human Genome Organisation convention.

CURRENT PRECISION MEDICINE APPROACHES IN SEPSIS

A clear indication of the usefulness of a described phenotype/endotype is whether it confers opportunity to prognostically and/or predictively enrich. Arguably, as several existing risk-based tools already prognosticate sepsis, novel phenotypes should offer information beyond prognostication and enable predictive enrichment, where the defining trait of the phenotype is responsive to a targeted therapy, a concept referred to as a "treatable trait" (53). Several different data types and algorithms have been used for phenotyping in sepsis; however, for conciseness, our review is mostly limited to multivariate approaches in adult sepsis with robust external validation.

Clinical Data

The availability of vast clinical data from the electronic health record (EHR) offers enormous opportunity to discover novel phenotypes in sepsis. In a large EHR-derived cohort, Seymour et al (54) identified and validated four phenotypes applying advanced statistical clustering methods clustering on 29 variables. The α-phenotype was the largest and had the least organ failure and mortality; the β-phenotype had older patients with more chronic illness and renal dysfunction; γ-phenotype patients were more inflamed and febrile; and the δ-phenotype was the least prevalent, with the highest lactate, liver dysfunction, and mortality. In a subset of patients, they found that the phenotypes had distinct protein signatures. Importantly, in secondary analysis of the Protocolized Care for Early Septic Shock (ProCESS) trial, that tested the efficacy of early goal directed therapy in sepsis, they observed significant heterogeneity of treatment effect (HTE) in the δ and γ phenotypes. While this work highlights the potential for identifying clinically relevant phenotypes using EHR data, challenges such as missingness and lack of intuitive clinical/biological correlates may have limited their implementation.

Kudo et al (55) applied a clustering algorithm to readily available coagulopathy markers such as platelet counts, prothrombin time/international normalized ratios, fibrinogen, fibrinogen/fibrin degradation products, D-dimer, and antithrombin activity, to identify four coagulopathy phenotypes of sepsis. The dA phenotype had severe coagulopathy, organ dysfunction, and increased mortality, dB had severe organ dysfunction with moderate coagulopathy, dC had moderate

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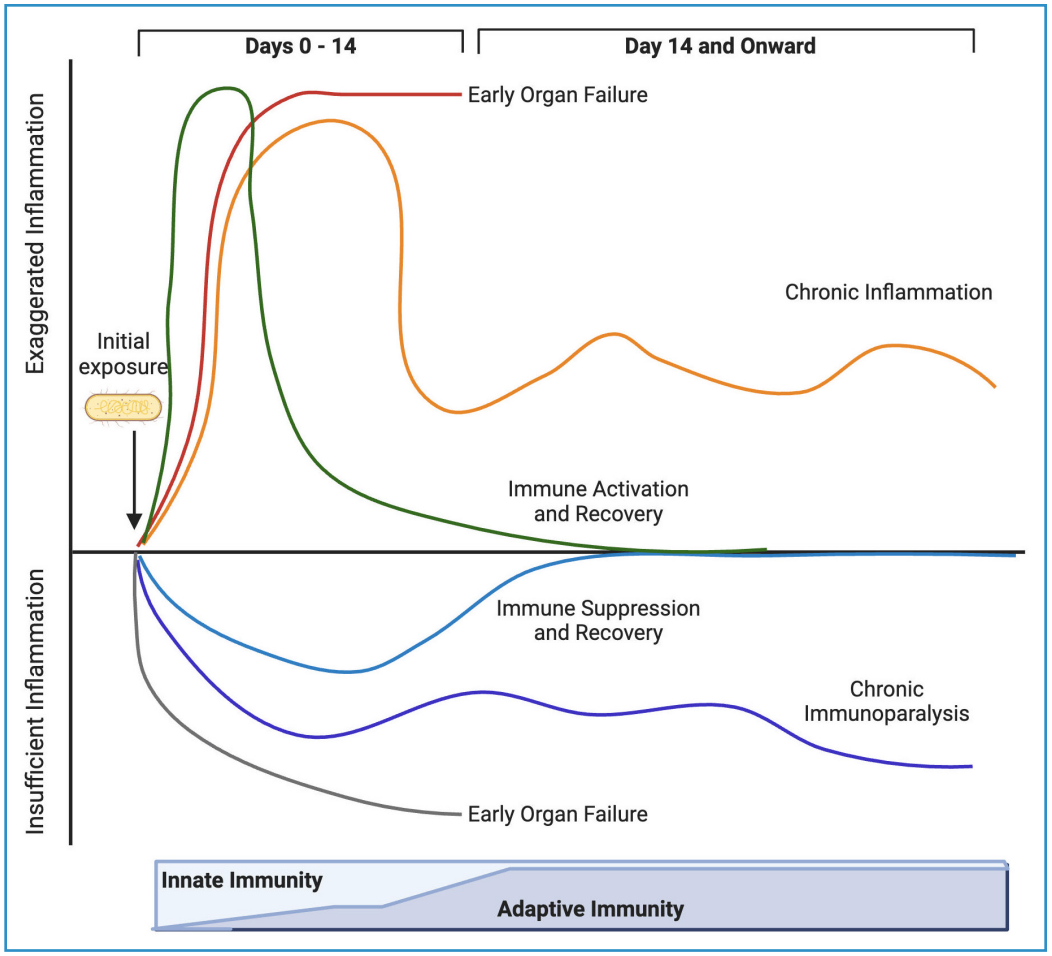

Figure 2. Temporal kinetics of the host response stratified by the exaggerated immune activation and immunosuppressive paradigms (46, 47).

disease with coagulopathy, and dD had mild disease without coagulopathy. Within the limits of an observational study without protocolized therapy, recombinant thrombomodulin was associated with benefit only in dA patients. To enable prospective testing, the investigators developed a web-based tool to predict dA phenotype for a precision-guided trial (56), exemplifying a discovery-to-implementation pathway for such analyses.

Other investigators have leveraged longitudinal data from the EHR to identify clinical phenotypes of sepsis. Using group-based trajectories modeling on longitudinal temperature data over the first 72 hours of sepsis, Bhavani et al (57) identified four subgroups called "hyperthermic, slow resolvers" (HSRs), "hyperthermic, fast resolvers" (HFRs), "normothermic," and "hypothermic." Hypothermic patients were older with more comorbidities, lower inflammatory markers, and highest mortality, HSR patients were youngest with the highest C-reactive protein (CRP) levels, and HFR patients had the best outcomes. These phenotypes have subsequently been shown to be associated with neutropenic septic shock (58) and *Staphylococcus aureus* bacteremia (59). They also found an association with the phenotypes and longitudinal kinetics of cytokine levels (59). While temperature-trajectory phenotypes are clinically intuitive, a major drawback is that they are reliant on several days' worth of data for classification, which may be a barrier to their implementation. Extending their work through the addition of other vital signs to this modeling approach (60), the same investigators identified four phenotypes of sepsis in a large training set (n = 12,473) and validated their findings externally (n = 8,256). They observed significant HTE in the secondary analysis of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) trial that tested the efficacy of balanced crystalloid vs. saline solution resuscitation, with balanced solution resulting in lower mortality in the phenotype characterized by low temperatures, normal heart rate, normal respiratory rate, and hypotension (group D) (61). Importantly, the algorithm can identify phenotypes using only 8 hours' worth of data, which has enabled a randomized controlled trial that is currently testing balanced crystalloids vs. saline in group D patients (n = 2000) (62). A final limitation of EHR-derived phenotypes is a lack of clear biological underpinning, which makes interventional choices beyond supportive care challenging when designing future trials.

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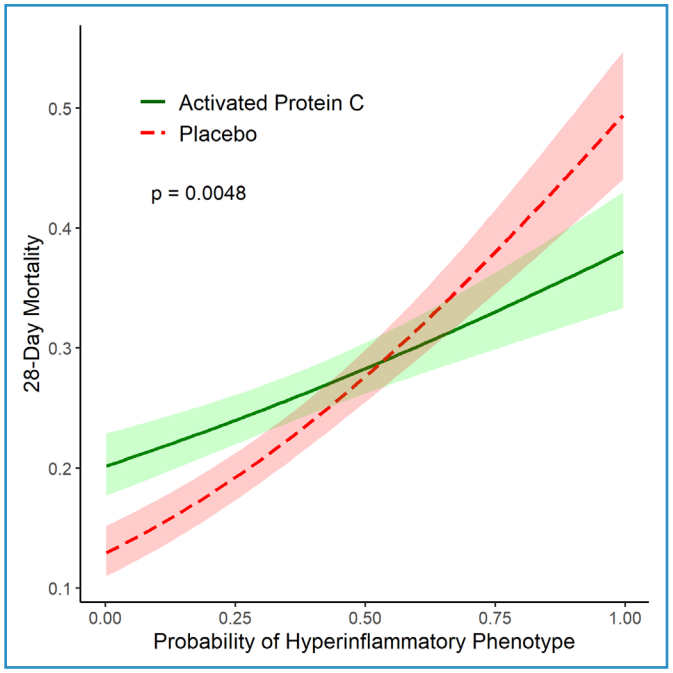

Figure 3. Differential treatment response to activated protein C in the hyperinflammatory and hypoinflammatory phenotypes, presented as a continuous probability generated by the clinical classifier model, in the secondary analysis of the Protein C Worldwide Evaluation in Severe Sepsis–Shock (PROWESS-SHOCK) trial (67). The *red line* represents the relationship of the probability of belonging to the hyperinflammatory phenotype and mortality in the placebo groups. The *green line* shows that the activated protein C treatment modulates this relationship with increased mortality in the hypoinflammatory phenotype and decreased mortality in the hyperinflammatory phenotype. *p* value is for the coefficient of the interaction term of phenotype probability and treatment group with 28-d mortality as the dependent variable.

Protein Biomarkers

Protein markers have previously been used alongside clinical data to identify two distinct phenotypes of acute respiratory distress syndrome (ARDS), termed *hyperinflammatory* and *hypoinflammatory* (63–66). Recently, the same two phenotypes were identified in two large observational cohorts of critically ill patients with sepsis (67). Further, using the clinical classifier model in the Protein C Worldwide Evaluation in Severe Sepsis–Shock (PROWESS-SHOCK) trial, investigators observed significant HTE with activated protein C, with harm in the Hypoinflammatory and benefit in the Hyperinflammatory phenotype (**Fig. 3**) (67). In the same study, independently, in analyses across three sepsis cohorts, the hyperinflammatory phenotype had significantly higher prevalence of bacteremia (approximately 30% vs. 12–15%), and *Enterobacteriaceae* was the predominant species (67). In a follow-up study, using plasma metagenomic sequencing in critically ill sepsis patients, the same investigators observed higher overall microbial DNA mass, lower overall species diversity, and higher abundance of *Enterobacteriaceae* species in the Hyperinflammatory phenotype compared with the Hypoinflammatory phenotype (68). Taken together, these findings implicate pathogens, both gut-derived and in general, as potential mediators of the Hyperinflammatory phenotype, and echo the theory of the gut being the motor of multiple organ failure in critical illness (69–71). Despite the phenotypes being reproduced in multiple cohorts, prospective demonstration of their clinical utility is lacking.

In another study, investigators described an interferon-gamma (IFN-γ)-driven sepsis subtype (IDS) (72). They diagnosed IDS based on chemokine (C-X-C motif) ligand 9 (CXCL9) levels greater than 2200 pg/mL and IFN-γ levels greater than 3 pg/mL, which they validated in a hold-out set. According to this schema, IDS had a prevalence of 20% and was associated with increased risk of death. The evidence for the pathophysiological implication of this phenotype or whether the phenotype is truly driven by IFN-γ, as is intimated by its name, was absent from these studies; nevertheless, IDS may be promising for prognostication. Other notable limitations of the IDS schema are that its diagnostic cutoffs are arbitrary and that its prospective evaluation is contingent on real time point-of-care quantification of CXCL9 and IFN-γ. Notably, given the low concentration cutoff value for IFN-γ, it is probable that a highly sensitive assay would be needed.

Transcriptomics

Transcriptomics, the study of high dimensional messenger RNA to capture gene expression, has also highlighted the heterogeneity in individual responses to infection. The first challenge in applying transcriptomics to sepsis is to select which tissue to profile. In sepsis, the site of infection is frequently either inaccessible for biopsy or the risk of sampling tissues is unacceptable. Thus, most sepsis transcriptomic studies have focused on whole blood or specific circulating leukocyte sampling. Circulating leukocytes reveal an integrated immune response and are highly accessible via a blood draw. While RNA profiling of blood cells

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has yielded important insights, an approach focused on circulating leukocytes has limitations, as it cannot fully capture responses that may be restricted to tissues such as the vasculature, epithelium, mesenchyme, or tissue-resident immune cells.

Several groups have identified reproducible patterns of whole blood gene expression that are prognostic and yet not easily predicted using clinical and physiologic data (73–77). The earliest work in this space was led by Wong et al (76, 77) in pediatric sepsis. Wong et al (78) also extended their observations from humans to animal models that culminated in potential traits of bacterial burden and host inflammation that could be targeted experimentally. In adults, Davenport et al (74) identified two transcriptomic sepsis response signature (SRS) clusters, SRS1 and SRS2, based on hypervariable whole blood gene. SRS1 was associated with higher mortality despite lower age, with gene expression suggestive of immune suppression, including endotoxin tolerance, T-cell exhaustion, and human leukocyte antigen (HLA) class II down-regulation (74).

This work evolved into a machine learning-derived quantitative SRS (SRSq) score based on 19 transcripts, offering a continuous measure of immune dysregulation (79). Higher SRSq scores correlated with worse outcomes, mediated by hypotension, renal failure, and coagulopathy. Single-cell RNA sequencing revealed enrichment of immunosuppressive immature neutrophils and $CD14^+$ monocytes termed "monocyte state 1" (MS1) in high SRSq patients (79). When co-cultured, these immature neutrophils seemed to promote systemic immunosuppression by inhibiting CD4+ T-cell activation (80). Subsequent transcriptomic sepsis studies have thus led to several candidate traits (SRSq, immature neutrophil populations, MS1 proportion) and specific dysregulated pathways (emergency granulopoiesis, *STAT3* dysregulation) that warrant investigation as potential treatable traits (81–83).

In a subgroup analysis of the Vasopressin vs Noradrenaline as Initial Therapy in Septic Shock (VANISH) trial, a randomized factorial trial that compared two vasopressor regimens in one arm and hydrocortisone vs. placebo in the other, participants with an SRS2 signature exhibited higher mortality when randomized to hydrocortisone (84). Although provocative, these results must be considered preliminary, as the subgroup analysis included only 176 patients and only 60 were included in the SRS2 hydrocortisone vs. placebo analysis (84). In an observational study of pediatric sepsis, for which the transcriptional subtypes minimally overlap with clusters discovered in adult sepsis populations (85), corticosteroid treatment was independently associated with mortality among patients classified to higher risk endotype A (86). Given significant differences in the leukocyte expression of both innate and adaptive immune programs, there is strong interest to test whether gene expression acts as a predictive biomarker for host immune-directed sepsis therapies. Despite the promising findings, the translation of transcriptional sepsis phenotypes to the bedside is currently a work in progress and remains a key challenge for this approach.

In a first-of-its-kind study, van Amstel et al (87) assessed concordance among clinical-, protein-, and transcriptomic-derived sepsis phenotypes in 522 patients from the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) cohort. Patients were assigned to EHR-derived (α, β, γ, δ), molecular (hyperinflammatory/hypoinflammatory), MARS1–4, and SRS phenotypes. Interestingly, these phenotyping schemes were discordant, suggesting that the clinical and biological information derived from each may be orthogonal to the other. This has important implications because it may allow further discrimination for each of these schemes; for example, SRS signatures in the hypoinflammatory and hyperinflammatory phenotypes may have divergent implications. Notably, EHR-derived phenotypes showed the least reproducibility, with less than 2% of patients assigned to α or β types, compared with ~20% in the original study (54), raising questions about cohort specificity (MARS vs. original study) and/or the inherent stability of EHR-based phenotyping.

Genome Studies

To date, genetics have mostly helped to elucidate the biologic mechanisms contributing to sepsis outcomes rather than advancing treatments that are predicated on a genotype or polygenic risk score. A genomic approach known as Mendelian randomization (MR) has also been applied to infer which plasma or serum markers exert a causal effect on sepsis incidence or survival (88, 89), which could prioritize therapeutic approaches.

During the COVID-19 pandemic, large-scale collaborations across the globe led by the Genetics Of

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Mortality In Critical Care (GenOMICC), International Severe Acute Respiratory and emerging Infection Consortium – Coronavirus Clinical Characterisation (ISARIC4C), and Spanish COalition to Unlock Research on host GEnetics on COVID-19 (SCOURGE) consortiums amassed more than 24,000 individuals with critical COVID-19 for genome-wide analysis/sequencing and revealed strong reproducible associations for more than 49 genetic variants (90). Further, by linking blood monocyte RNA expression with DNA genotyping, MR analysis suggested 15 proteins causally linked to the development of critical COVID-19, including proteins that influence virus entry or replication as well as those interacting with immune activation and vascular regulation (90). Functional genomic analysis of missense variants in the *TYK*, *SFTPD*, and *SLC22A31*, and in the case of *TYK*, provided strong rationale to test Janus Kinase inhibitors such as baricitinib (90, 91). Clinical trials subsequently found baricitinib to significantly improve outcomes for patients with COVID-19 and critical illness (92–94). Of note, compared with the nonspecific diagnosis of sepsis, COVID-19 was a relatively homogeneous monopathogenic disease, which coupled with an unprecedented large volume of cases, increased the probability of discovering abnormal variants.

Functional Immune Assays

The complex, context-specific host response in sepsis limits the utility of single measurements. Functional immune assays, which assess an individual's response to inflammatory or infectious stimuli, may offer a more integrated view. For example, monocytes stimulated with endotoxin show marked variability in cytokine production across individuals (95, 96). The proportion of monocytes expressing the antigen HLA-DR are known to correlate with endotoxin tolerance, or a low inflammatory response to endotoxin (97, 98). In a pilot trial of 38 sepsis patients with low monocyte HLA-DR, granulocyte–macrophage colony-stimulating factor improved HLA-DR expression and reduced ventilation duration and hospital stay (99). The same treatment, however, was ineffective in a larger unenriched trial in ARDS patients (n = 130) (100), leading some to consider whether the failure to target low HLA-DR monocyte patients might explain these disparate results.

More recently, the Personalized Randomized trial Of Validation and restoration of Immune Dysfunction in severE infections and Sepsis (PROVIDE) trial attempted to personalize immune-directed therapies to patients' immune response during sepsis, and planned to treat low monocyte HLA-DR participants with recombinant IFN-γ to reverse immunoparalysis (101). Despite a critically ill population with high mortality, only two of 240 patients met the proposed immunoparalysis threshold of fewer than 30% $CD14^+$ monocytes expressing HLA-DR (101), highlighting the challenges of such precision medicine trials. As an alternative functional immune assay, investigators tested the IFN-γ production of T lymphocytes in whole blood drawn from patients with sepsis, noninfectious critical illness, or healthy volunteers using a technique known as enzyme-linked immunosorbent spot assay and observed that sepsis nonsurvivors consistently exhibited lower resting and stimulated IFN-γ production (102). As trials to overcome sepsis-induced immune suppression continue to be proposed (26), future trials may test whether functional immune assays have predictive utility.

FUTURE DIRECTIONS FOR PRECISION MEDICINE IN SEPSIS

A common challenge across multivariate/multidimensional phenotypes is how to identify them rapidly at the bedside to enable real time decision-making. An additional consideration is determining how infrequent a phenotype can be before its low prevalence undermines clinical implementation, which depends on the phenotype's association with the outcome of interest, the strength of that association, and the efficacy of available interventions in modifying the outcome.

Several clinical trials have begun to tackle these questions. The Targeted Reversal of Inflammation in Pediatric Sepsis trial (NCT05267821) is an exciting platform trial in pediatric sepsis where patients are immunophenotyped at a central site on day 2 of multiple organ failure. The immunophenotype includes a whole blood functional assay with lipopolysaccharide stimulation followed by TNF-α level measurements, and ferritin and CRP quantification. Patients without immunoparalysis, defined as post-stimulation TNF-α less than 200 pg/mL and serum ferritin 500–2000 ng/mL or serum CRP greater than or equal to 4 mg/dL, or serum ferritin greater than or equal to 2000 ng/mL regardless of simulated TNF-α response, will be randomized to either IV anakinra or placebo. This study

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is an excellent example of operationalizing complex biological measurements to make treatment decisions. In adults, the Precision medicine Adaptive platform Network Trial in Hypoxaemic acutE respiratory failure (PANTHER) consortium (https://panthertrial.org) has begun recruitment evaluating therapies in the hypoinflammatory and hyperinflammatory phenotypes in ARDS and acute respiratory failure, a majority of these patients will likely meet sepsis criteria. Notably, the phenotypes will be allocated at the bedside using a validated point-of-care multiplex assay (103, 104).

Beyond clinical trials, the ongoing multicenter ARDS, pneumonia, and sepsis consortium (https://apsconsortium.org/) funded by the U.S. National Institute of Health, is collecting detailed longitudinal biospecimens and clinical data from 4000 critically ill patients to investigate mechanisms underlying sepsis phenotypes. Such large-scale human studies are essential to address sepsis heterogeneity and identify novel treatable traits. Identifying robust, biologically defined phenotypes may shift the paradigm in sepsis from syndrome-based to a disease-centric framework, enabling mechanistic studies in animal models (105), genome-wide association and epigenetic studies (106, 107), ultimately accelerating the discovery of clinically translatable targets.

SUMMARY

Sepsis presents clinically and biologically as a highly heterogeneous syndrome; however, recent advances in phenotyping using clinical, molecular, and immunological data show promise in identifying more homogeneous subgroups that may be differentially responsive to therapies. Coupled with technological advances in data analytics, diagnostics, point-of-care testing, and trial design, it would be fair to surmise that sepsis is on the brink of an era of precision medicine. Collaboration with healthcare workers, patient partnerships, and sustained funding will be critical to meet these challenging but achievable goals.

1 *Department of Medicine, Massachusetts General Hospital, Boston, MA.*

2 *Division of Pulmonary, Allergy, and Critical Care Medicine, Center for Translational Lung Biology, Lung Biology Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

3 *Division of Clinical and Translational Research, Division of Critical Care, Department of Anesthesia, Washington University, St. Louis, MO.*

Supported, in part, by the GM142992, HL173531 (to Dr. Sinha); R38HL150212 (to Dr. Gay); and HL161196, HL168892, HL168419 (to Dr. Meyer).

Dr. Gay's institution received funding form the National Heart, Lung, and Blood Institute (R38HL150212). Drs. Gay and Sinha received support for article research from the National Institutes of Health. Dr. Meyer's institution received funding from Quantum Leap Healthcare Collaborative; she received funding from Novartis. Drs. Meyer and Sinha received funding from AstraZeneca. Dr. Sinha received funding from Prenosis.

For information regarding this article, E-mail: p.sinha@wustl.edu

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